Objections to the Specification

The Examiner stated that the lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. The Applicant has checked the specification and is not aware of any errors to be corrected.

The Examiner further states that the application does not contain an Abstract of the disclosure as required by 37 C.F.R. § 1.72(b). An Abstract is attached hereto as "Appendix A." Accordingly, Applicants respectfully request the Examiner to withdraw the objections to the Specification.

Claims Objections

The Examiner objects to Claims 1, 9, 12, and 18 because the claims contain several periods. As amended, Claims 1, 9, 12, and 18 each contain only one period. Accordingly, Applicants respectfully request the Examiner to withdraw the claim objections.

Rejections under 35 U.S.C. § 112

The Examiner rejected Claims 1-19 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner particularly points out that Claims 1, 9, 12, and 18 recite claim limitations that are contained within square brackets and parentheses. As amended, Claims 1, 9, 12, and 18 do not contain square brackets and parentheses.

The Examiner rejected Claims 11 and 19 under 35 U.S.C. § 112, second paragraph for reciting "Formula (I)" but failing to define "Formula (I)." As amended, Claims 11 and 19 define "Formula (I)".

The Examiner rejected Claim 15 under 35 U.S.C. § 112, second paragraph for reciting "climacteric and post-climacteric diseases." As amended, Claim 15 recites "menopausal or post-menopausal."

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejections under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 103

The Examiner rejected Claims 1-11 under 35 U.S.C. § 103(a) as being unpatentable over Mizutani et al. (Biochemical and Biophysical Research Communications 1998, 253, pages 859-863) and further in view of Caspar et al. (WO 00/38620-A2) and further in view of Tortora et al. (WO 00/64282-A1).

Mizutani et al. discloses the effect on ALP (Alkaline Phosphatases) activity of treatment of osteoblastic (bone forming) MC3T3-E1 cells with resveratrol. Mizutani et al. further discloses the use of resveratrol for the treatment of osteoporosis.

Caspar et al. discloses a composition and method for treating periodontal disease with resveratrol in combination with a pharmaceutically acceptable carrier.

Tortora et al. was filed on April 27, 2000, whereas the present application claims priority to a PCT application that was filed on January 29, 2000. Therefore, Tortora et al. does not qualify as prior art.

Claim 1 recites, *inter alia*, a composition for preventing or treating a disease accompanied by a decrease in bone weight, the composition comprising a pharmaceutically acceptable carrier and, as an active component, at least one member selected from a compound represented by Formula (1), wherein the disease accompanied by a decrease in bone weight is any of menopausal or post-menopausal diseases. Claim 11 recites, *inter alia*, a method for preventing or treating diseases accompanied by a decrease in bone weight by taking or administrating an effective amount of at least one member selected from the compound represented by Formula (I) or a multimer thereof.

According to M.P.E.P. 2143.01, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

Although Mizutani et al. discloses the effect on ALP activity of treatment of osteoblastic MC3T3-E1 cells with resveratrol, Mizutani et al. merely discloses the results of *in vitro* experiments using osteoblastic cells and resveratrol. Mizutani et al. does not disclose or suggest that stilbene-type compounds are effective in preventing or treating diseases accompanied by a

decrease in bone weight in complicated living organisms, especially during menopausal and post-menopausal periods. Additionally, Mizutani et al. does not disclose or suggest that stilbene-type compounds could be combined with a pharmaceutically acceptable carrier, as recited in Claim 1.

Furthermore, a composition having an effect on ALP activity *in vitro* is not always useful to prevent or treat diseases accompanied by a decrease in bone weight. Enclosed with this Amendment as Appendix "B" is a reference (JJ. Stepan et al. Clinica Chimica Acta, 151 (1985) 273-283) showing no relationship between the effect on ALP activity and its link to preventing or treating osteoporosis. In Figure 1 of Stepan et al., a significant peak occurs between the ages of 50 and 60 in the scattergrams of bone isoenzyme of serum ALP. Therefore, if there were a relationship between the effect on ALP activity and its link to preventing or treating osteoporosis, the occurrence of osteoporosis should decrease at ages 50-60 in females. However, the occurrence rate of osteoporosis increases for the older population and dramatically rises in post-menopausal women, as stated in the Specification at page 2, lines 13-15. Therefore, there is no relationship between the effect on ALP activity and its link to preventing or treating osteoporosis. In this manner, Mizutani et al., taken with the literature in the field that is accessible to one of ordinary skill in the art, does not provide motivation or suggestion to use resveratrol for the prevention or treatment of a disease accompanied by a decrease in bone weight, in which the disease is menopausal or post-menopausal.

Even though Casper et al. discloses the use of resveratrol for the treatment of periodontal disease, Casper et al. merely discloses the results of *in vitro* experiments using resveratrol. Casper et al. focuses on using resveratrol as a aryl hydrocarbon receptor (AhR) antagonist. On page 2, lines 12-24, Casper et al. discloses that as an AhR antagonist, resveratrol is useful generally to prevent the toxic effects of environmental exposure to AhR ligands. AhR antagonists may be useful to block stimulation of IL-1β and TNF-α, thereby minimizing some symptoms of periodontal disease.

Casper et al. teaches the prevention of periodontal disease through a specific mechanism involving AhR. Casper et al. does not teach or suggest the use of a composition containing stilbene-type compounds as defined in Claim 1 for preventing or treating a disease accompanied

by a decrease in bone weight, in which the disease is menopausal or post-menopausal. Since AhR and menopausal and post-menopausal diseases are not related to each other, one of ordinary skill in the art would not be motivated to use the compositions of Casper et al. to prevent or treat a disease that is menopausal or post-menopausal.

Therefore, regarding Claims 1-11, there is no suggestion or motivation in the prior art to use compositions as defined in Claim 1 to prevent or treat a disease accompanied by a decrease in bone weight, in which the disease is menopausal or post-menopausal.

The Examiner rejected Claims 12-19 under 35 U.S.C. § 103(a) as being unpatentable over Mizutani et al. (Biochemical and Biophysical Research Communications 1998, 253, pages 859-863) and further in view of Toppo et al. (U.S. Patent No. 6,048,903) and further in view of Totoro et al. (WO 00/64282-A1).

As mentioned above, Mizutani et al. discloses the effect on ALP (Alkaline Phosphatases) activity of treatment of osteoblastic (bone forming) MC3T3-E1 cells with resveratrol. Mizutani et al. further discloses the use of resveratrol for the treatment of osteoporosis.

Toppo et al. teaches a level of heavy density lipoproteins (HDL) in the blood of a human subject can be increased by administering trans-resveratrol to the subject daily.

As mentioned above, Tortora et al. was filed on April 27, 2000, whereas the present application claims priority to a PCT application that was filed on January 29, 2000. Therefore, Tortora et al. does not qualify as prior art.

Claims 12 and 19 disclose, *inter alia*, a composition and method for preventing and treating hypertension or a disease resulting from hypertension, the composition containing, as an active component, at least one member selected from the compound represented by Formula (1)or a multimer thereof.

As mentioned above, according to M.P.E.P. 2143.01, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

Mizutani discloses that resveratrol inhibits oxidation of low density lipoprotein (LDL), preventing atherosclerotic changes as well as exhibiting vasorelaxing activity in the isolated aorta of a rat, and is presumably, useful for the treatment of hypertension. However, a composition for inhibiting the oxidation of LDL is not always useful for the treatment of hypertension. We enclose as Appendix "C" a reference (Fruebis et al. J. Clin. Invest., vol. 94, p 392-398, 1994) that shows LDL resistance to oxidation must reach some threshold level before there is significant protection atherogenesis.

Then, the Examiner believes that Toppo et al. teaches a link between hypercholestemia and hypertension and the effect that resveratrol has on HDL/LDL levels. However, even if HDL were a high level, there is a possibility to contract coronary heart disease, which results from hypertension. Enclosed herewith as Appendix "D" is a reference (Jikken Igaku, Experimental Medicine, vol. 6, no. 14, 1988, pages 125-132) and an English translation of a relevant portion (page 130, left column, lines 9-11). Igaku shows cases of presence of both hyper-high density lipoproteineamia and coronary disease at the same time. In view of Igaku, Toppo et al. does not provide motivation to use the composition of Claim 12 as a preventative or therapeutic composition for hypertension and diseases resulting from hypertension.

Therefore, regarding Claims 12-19, there is no suggestion or motivation in the prior art to use compositions as defined in Claim 12 to prevent or treat hypertension or a disease resulting from hypertension.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejections under 35 U.S.C. § 103(a).

New Claims

New Claims 20-29 are directed to methods of using the composition. The new claims are supported by the existing claims and specification and claims as filed. Accordingly, there is no addition of new matter.

CONCLUSION

In view of the foregoing amendments and comments, it is respectfully submitted that the present application is fully in condition for allowance, and such action is earnestly solicited.

The undersigned has made a good faith effort to respond to the all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned in order to resolve such issue promptly.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 7-17-02

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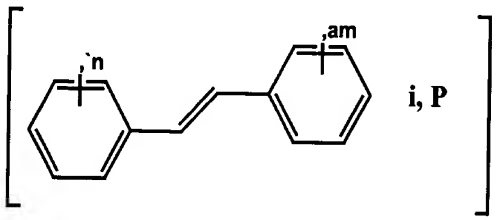
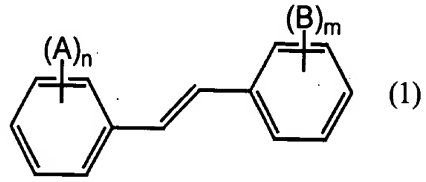
VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please cancel Claim 4 without prejudice.

Please amend Claims 1, 9, 11, 12, 15, 18, and 19 as follows:

1. (Amended) A composition for preventing or treating a disease accompanied by a decrease in bone weight, the composition **[containing]** comprising a pharmaceutically acceptable carrier and, as an active component, at least one member selected from a compound represented by Formula (1) or a multimer thereof:





(1)

[[]wherein A and B are the same or different and **[each represents a]** are independently selected from the group consisting of halogen **[atom]**, **[an]** amino **[group]**, **[an]** amidino **[group]**, **[an]** anilinoamide **[group]**, **[a]** mercapto **[group]**, **[a]** sulfonic acid **[group]**, **[a]** phosphate **[group]**, **[a]** carboxy **[group]**, **[a]** hydroxy C_1-C_5 alkyl **[group]**, **[a]** sugar residue, -OR^1 **[(R^1 represents a hydrogen atom, a C_1-C_5 alkyl group, a hydroxy C_1-C_5 alkyl group or a C_2-C_5 alkenyl.) or]**, and –$OCOR^2$ **[(R^2 represents a C_1-C_5 alkyl group, a hydroxy C_1-C_5 alkyl group or a C_2-C_5 alkenyl group.).]**;

wherein R^1 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, hydroxy C_1-C_5 alkyl, and C_2-C_5 alkenyl; and

R^2 is selected from the group consisting of C_1-C_5 alkyl, hydroxy C_1-C_5 alkyl, and C_2-C_5 alkenyl;

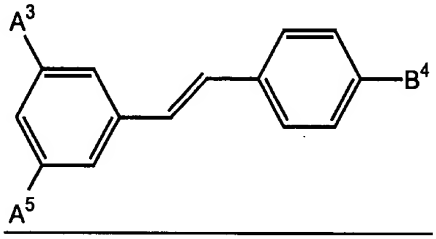
[n and m are the same or different and each is an integer from 0 to 5. There are n A's and m B's each of which may be the same or different.] and its multimers]

n is number of substituents A present and is a number from 0 to 5; and

m is number of substituents B present and is a number from 0 to 5; and

wherein the disease accompanied by a decrease in bone weight is any of menopausal or post-menopausal diseases.

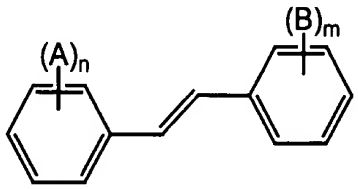
9. (Amended) The composition according to Claim 1, wherein the compound represented by Formula (1) **[has substituents at least positions 3, 5 and 4', the substituents being]** is substituted at least as follows:



wherein A^3, A^5, and B^4 are the same or different and **[any one of]** are independently selected from the group consisting of **[a]** hydroxyl **[group]**, **[a]** sugar residue, and $-OCOR^2$ **[[R2 is as defined in the above.]]**;

wherein R^2 is selected from C_1-C_5 alkyl, hydroxy C_1-C_5 alkyl, and C_2-C_5 alkenyl.

11. (Amended) A method for preventing or treating diseases accompanied by a decrease in bone weight by taking or administrating an effective amount of at least one member selected from the compound represented by Formula (1) **[and its multimers]** or a multimer thereof:



(1)

wherein A and B are the same or different and are independently selected from halogen, amino, amidino, anilinoamide, mercapto, sulfonic acid, phosphate, carboxy, hydroxy C_1-C_5 alkyl, sugar residue, -OR^1, and –$OCOR^2$;

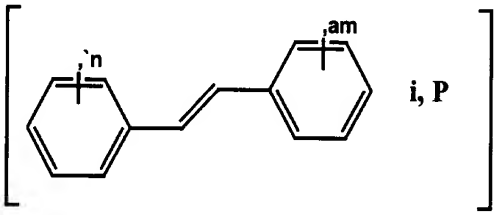
wherein R^1 is selected from hydrogen, C_1-C_5 alkyl, hydroxy C_1-C_5 alkyl, and C_2-C_5 alkenyl; and

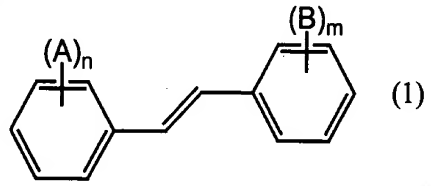
R^2 is selected from C_1-C_5 alkyl, hydroxy C_1-C_5 alkyl, and C_2-C_5 alkenyl;

n is number of substituents A present and is a number from 0 to 5; and

m is number of substituents B present and is a number from 0 to 5.

12. (Amended) A preventative or therapeutic composition for hypertension or a disease resulting from hypertension, the composition containing, as an active component, at least one member selected from the compound represented by Formula (1) or a multimer thereof:





(1)

[[]wherein A and B are the same or different and **[each represents a]** are independently selected from the group consisting of halogen **[atom]**, **[an]** amino **[group]**, **[an]** amidino **[group]**, **[an]** anilinoamide **[group]**, **[a]** mercapto **[group]**, **[a]** sulfonic acid **[group]**, **[a]** phosphate **[group]**, **[a]** carboxy **[group]**, **[a]** hydroxy C_1-C_5 alkyl **[group]**, **[a]** sugar residue, -OR^1 **[(R^1 represents a hydrogen atom, a C_1-C_5 alkyl group, a hydroxy C_1-C_5 alkyl group or a C_2-C_5 alkenyl.) or]**, and –$OCOR^2$ **[(R^2 represents a C_1-C_5 alkyl group, a hydroxy C_1-C_5 alkyl group or a C_2-C_5 alkenyl group.).]**;

wherein R^1 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, hydroxy C_1-C_5 alkyl, and C_2-C_5 alkenyl; and

R^2 is selected from the group consisting of C_1-C_5 alkyl, hydroxy C_1-C_5 alkyl, and C_2-C_5 alkenyl;

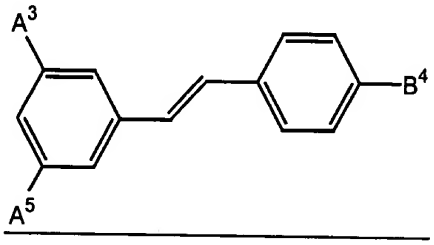
[n and m are the same or different and each is an integer from 0 to 5. There are n A's and m B's each of which may be the same or different.] and its multimers]

n is number of substituents A present and is a number from 0 to 5; and

m is number of substituents B present and is a number from 0 to 5.

15. (Amended) The composition according to Claim 12, wherein the hypertension and diseases resulting from hypertension **[are climacteric and post-climacteric diseases]** is present in menopausal or post-menopausal period.

18. (Amended) The composition according to Claim 12, wherein the compound represented by Formula (1) **[has substituents at at least positions 3, 5 and 4', the substituents being]** is substituted at least as follows:

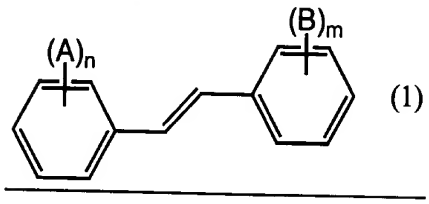


wherein A^3, A^5, and B^4 are the same or different and **[any one of]** are independently selected from the group consisting of **[a]** hydroxyl **[group]**, **[a]** sugar residue, and $-OCOR^2$ **[[R2 is as defined in the above.]]**;

wherein R^2 is selected from C_1-C_5 alkyl, hydroxy C_1-C_5 alkyl, and C_2-C_5 alkenyl.

19. (Amended) A method for preventing or treating hypertension and diseases resulting from hypertension by taking or administrating an effective amount of at least one

member selected from the compound represented by Formula (1) **[and its multimers]** or a multimer thereof:



(1)

wherein A and B are the same or different and are independently selected from halogen, amino, amidino, anilinoamide, mercapto, sulfonic acid, phosphate, carboxy, hydroxy C_1-C_5 alkyl, sugar residue, -OR^1, and –$OCOR^2$;

wherein R^1 is selected from hydrogen, C_1-C_5 alkyl, hydroxy C_1-C_5 alkyl, and C_2-C_5 alkenyl; and

R^2 is selected from C_1-C_5 alkyl, hydroxy C_1-C_5 alkyl, and C_2-C_5 alkenyl;

n is number of substituents A present and is a number from 0 to 5; and

m is number of substituents B present and is a number from 0 to 5.

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